White Matter Hyperintensities and Subclinical Infarction
Associations With Psychomotor Speed and Cognitive Flexibility

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Background and Purpose—We examined white matter hyperintensity volume (WMHV) and subclinical infarction (no history of clinical stroke; SI) in relation to performance on tests of sequencing, cognitive flexibility, and sensorimotor ability.

Methods—The Northern Manhattan Study includes a stroke-free community-based sample of Hispanic, Black, and White participants. A subsample (n=656) has undergone measurement of WMHV, SI, and neuropsychological testing. Linear regression was used to examine WMHV and SI in relation to performance on tests of sequencing as measured by Color Trails 1, cognitive flexibility as measured by Color Trails 2, and sensorimotor ability as measured by Grooved Pegboard, using generalized estimating equations (GEE) to account for the correlation among the cognitive tests and other covariates.

Results—Considering performance on the tests of sequencing, cognitive flexibility, and sensorimotor ability simultaneously using GEE, WMHV and subclinical infarction were each associated with worse cognitive performance globally. There was a threshold effect for WMHV with those in the upper quartile performing significantly worse on the tests of cognitive flexibility and sensorimotor ability. Those with frontal SI performed worse on the test of cognitive flexibility and those with deep SI, worse on the test of sequencing.

Conclusions—Both SI and WMHV were associated with globally worse cognitive performance. Participants with WMH affecting more than 0.75% of cranial volume had significantly slower performance on a task of cognitive flexibility and sensorimotor ability than those in the lowest quartile. The effects of SI on cognitive performance varied by location. **(*Stroke*. 2008;39:800-805.)**

Key Words: leukoaraiosis ■ silent stroke ■ vascular cognitive impairment

Vascular cognitive impairment (VCI) is a term referring to cognitive dysfunction caused by cerebrovascular disease and encompasses a range of severity from the mildest changes to frank dementia. The causes of VCI are not well understood, but subcortical damage to white matter tracts is one.[1] White matter hyperintensities (WMH) are often found incidentally on Flair/T2-weighted brain MRI scans of clinically asymptomatic individuals and are ascribed to breakdown of the blood-brain barrier. They have been most strongly associated with ischemic damage because they are more common in people with vascular risk factors, are associated with an increased risk of stroke, and correspond to vascular disease and microangiopathy in vivo and in pathological studies.[2–5]

Growing evidence implicates WMH in cognitive functions, especially those mediated by the frontal lobes and including attention, psychomotor speed, and executive function, but the volume of injury sufficient to cause dysfunction is not known.[6,7] Many studies have estimated the amount of WMH using semi-quantitative visual rating scales that do not quantify the volume of damage. These methods also have limited interrater reliability, and the use of different scales has made comparison across studies difficult. Computerized methods now allow quantification of WMH volume (WMHV) and are beginning to show an even stronger relationship with cognitive function, but few studies have examined the dose effect.[8–11] Similarly, subclinical infarcts (infarcts in the absence of clinical stroke; SI) have been associated with an increased risk of dementia and cognitive decline.[12] However, the effects of SI in relation to WMH require further study as does the importance of anatomic location.

Vascular disease is common in the elderly, and so are degenerative causes of cognitive dysfunction such as Alzheimer disease. However, many studies have included only older

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subjects, making it difficult to separate the effects of WMH on cognition from primary neurodegeneration. Although it is not possible to eliminate this problem, population-based studies that include younger subjects are needed.[11] In addition, few studies have been carried out in multiethnic communities, especially those that include Hispanic and Black people who have more vascular risk factors that may cause WMH and SI, as well as a greater risk of stroke than Whites.[13]

This study examines the association between subclinical brain disease (WMHV and SI) and cognitive function. We hypothesized that increasing WMHV would be inversely associated with cognitive performance, and we examined both continuous and categorical (quartiles) measures of WMHV. We expected that subjects with SI would perform worse on selected cognitive tasks and that infarct location would have a domain-specific effect. We examined tests of sequencing and cognitive flexibility as measured by the Color Trails because of their demand on frontal-subcortical networks. We also examined performance on the Grooved Pegboard task as a test of sensorimotor integration and planning. Many studies that examined the effect of subclinical brain disease on cognition used statistical methods that do not consider the correlation among different cognitive tests. This may leave doubt when an association is found for several tests about the role played by shared variance. We therefore adjusted for the correlation among these tests and potential confounders in a population-based sample including Hispanic, Black, and White individuals, including younger participants likely to be in the earliest stages of VCI.

Methods

The Northern Manhattan Study (NOMAS) is a population-based cohort study that includes 3298 stroke-free participants identified using random digit dialing using dual-frame sampling to identify published and nonpublished telephone numbers. People were eligible if they never had been diagnosed with a stroke, were 40 years of age or older, and had been residents of Northern Manhattan for at least 3 months in a household with a telephone. Subjects from the telephone sample were recruited for in-person assessment and the overall response rate was 68%. Data were collected between 1993 and 2001 through interviews by trained bilingual research assistants using standardized data collection instruments, review of medical records, physical and neurological examinations by study physicians, and fasting blood samples for glucose and lipids measurements. Standardized questions about vascular risk factors were adapted from the Centers for Disease Control and Prevention Behavioral Risk Factor Surveillance System as defined previously.[14] Hypertension was defined as a systolic blood pressure >140 mm Hg or a diastolic blood pressure >90 mm Hg based on the mean of 2 blood pressure measurements, self-report of a diagnosis of hypertension, or medical treatment thereof. Diabetes was defined a fasting blood glucose ≥ 127 mg/dL, self-report of a diagnosis of diabetes, or insulin or oral hypoglycemic use. Cardiac disease was defined as a history of coronary artery disease, atrial fibrillation, or myocardial infarction. Race-ethnicity was based on self-identification as described previously.[14] Changes in health or vital status were determined through annual telephone follow-up.

MRI Examination

Subjects were enrolled into the MRI substudy using the following criteria: (1) age older than 50 years; (2) no contraindications to MRI; and (3) willing to sign informed consent. The study was approved by the Columbia University Institutional Review Board. Imaging was performed on a 1.5T MRI system (Philips Medical Systems) at the Columbia University Hatch Research Center. Analysis of WMHV was based on a Fluid Attenuated Inversion Recovery (FLAIR) image acquired in the Multi-Slice Turbo Spin Echo (MS-TSE) mode with a field of view of 250 mm, rectangular field of view of 80%, and an acquisition matrix of 192×133 scaled to 256×256 in reconstruction. The FLAIR image has a slice thickness of 3 mm with no gap, an echo time of 144 ms, a repetition time of 5500 ms, an inversion recovery delay of 1900 ms, and a flip angle of 90 degrees. Images were oriented parallel to a hypothetical line connecting the anterior and posterior commissures. For quantitative analysis of WMHV, MRI data were transferred to the University of California at Davis. Analyses were performed using the Quantum 6.2 package on a Sun Microsystems Ultra 5 workstation. All analyses were performed blind to subject personal identifying information.

White matter hyperintensity segmentation from surrounding tissue was performed in 2 steps according to previously reported methods.[15,16] Briefly, nonbrain elements were manually removed from the image by operator guided tracing of the dura mater within the cranial vault including the middle cranial fossa, but excluding the posterior fossa and cerebellum. The resulting measure of the cranial vault was defined as the total cranial volume to correct for differences in head size among subjects. Interrater reliabilities for the MRI measures of intracranial volume (0.97), brain volume (0.97), and WMHV (0.99) from images of this study were high. The first step in image segmentation required the identification of brain matter. Image intensity nonuniformities were then removed from the image and the corrected image was modeled as a mixture of 2 gaussian probability functions with the segmentation threshold determined at the minimum probability between these distributions.[16,17] Once brain matter segmentation was achieved, a single gaussian distribution was fitted to image data and a segmentation threshold for WMHV was determined a priori as 3.5 standard deviations (SDs) in pixel intensity above the mean of the fitted distribution of brain parenchyma as described previously.[15] Morphometric erosion of 2 exterior image pixels was also applied to the brain matter image before modeling to remove the effects of partial volume cerebrospinal fluid pixels on white matter hyperintensity determination. White matter hyperintensity volume was expressed as the proportion of total cranial volume to correct for head size and log transformed to create a normal distribution (log-WMHV) for analysis as a continuous measure. WMHV was also divided into quartiles to examine the dose effect of increasing WMHV on cognitive performance.

The presence or absence of brain infarcts (SI) on MRI was determined according to a protocol using the size, location, and imaging characteristics of the lesion.[18] The image analysis system allowed for superimposition of the subtraction image, the proton density image, and the T2-weighted image at 3 times magnified view to assist in interpretation of lesion characteristics. Signal void, best seen on the T2-weighted image, was interpreted to indicate a vessel. Lesions 3 mm or larger were considered brain infarcts. Other necessary imaging characteristics included (1) CSF density on the subtraction image and (2) whether the stroke was in the basal ganglia area, distinct separation from the circle of Willis vessels, and perivascular spaces.

Neuropsychological Testing

On the day of the MRI a neuropsychological battery was administered in a quiet room in either English or Spanish, based on the language spoken by the subject at home, by bilingual trained research assistants. We used 3 timed tests to detect cognitive dysfunction related to subclinical brain disease including a test of sequencing, 1 of cognitive flexibility and set switching, and 1 of sensorimotor ability. All of these tests draw on frontal-subcortical networks thought to be most effected in vascular cognitive disorders. To minimize cultural and educational bias, sequencing was assessed with Color Trails 1 and cognitive flexibility was assessed with Color Trails 2 (PAR).[19] The Color Trails tests do not incorporate letters from the alphabet and literacy is considered less of a factor in performance. Sensorimotor ability was assessed using the Grooved Pegboard (Lafayette Instruments). Participants were given 2.5 min-

Table 1. Characteristics of the Northern Manhattan MRI Sample, Overall, by Quartiles of White Matter Hyperintensity Volume (WMHV), and by Presence of Subclinical Infarction

	Overall (n=656)	Subclinical Infarction (n=104)	White Matter Hyperintensity Volume			
			Quartile 1 (n=164)	Quartile 2 (n=164)	Quartile 3 (n=164)	Quartile 4 (n=164)
Age, mean (SD)	70.4 (7.9)	72.3 (8.1)†	67.1 (7.0)	67.8 (6.7)	71.7 (7.2)*	75.0 (7.4)*
Women	59	13†	51	59	60	63†
Race-ethnicity						
Hispanic	61	14†	63	72	55	53†
Black	21	22	15	13	22	36†
White	18	14	21	15	23	11
Education, mean years	10.3 (5.0)	11.1 (4.6)	10.3 (5.1)	10.2 (5.3)	10.3 (5.0)	10.5 (4.6)
Hypertension	68	20†	59	61	72	78†
Diabetes	17	14	11	18	20	20†
Cardiac disease	16	19	13	15	16	19
MMSE, mean (SD)	27.0 (3.0)	27.0 (3.4)	27.6 (2.7)	27.1 (2.7)	26.9 (3.1)	26.6 (3.3)
Subclinical infarct	17	...	10	10	15	32†
WMHV, % cranial volume	0.6 (0.7)	0.7 (1.1)†	0.2 (0.04)	0.3 (0.04)	0.5 (0.1)	1.6 (0.9)‡
Cognitive performance						
Sequencing (sec)	83 (42)	92.8 (48.3)#	74 (39)	79 (40)	85 (41)	87 (39)
Cognitive flexibility (sec)	177 (71)	189.0 (74.7)#	161 (68)	171 (71)	181 (75)§	190 (67)#
Sensorimotor ability (sec)	114 (25)	120.4 (23.1)#	107 (23)	108 (25)	116 (25)	123 (24)#

Categories shown as percent unless otherwise noted.

†Chi Square or Student *t* test, $P<0.05$.

*Linear regression $P<0.05$ compared to lowest quartile of WMHV and adjusted for age (‡) and education (#); § $P<0.1$.

utes to complete the Grooved Pegboard with each hand, 4 minutes to complete the Color Trails 1, and 5 minutes to complete the Color Trails 2.

Statistical Analyses

We measured the association between both WMHV and SI in relation to cognitive performance using Chi Square tests and Student *t* tests to assess the effects of potential confounders. We examined WMHV in quartiles and as a continuous measure (log transformed to normalize the distribution=log-WMHV) and dichotomized SI into present or absent (few had more than one infarct). We used linear regression to examine WMHV and SI as predictors of each cognitive domain adjusting for age and education, creating z-scores from the raw timed scores for comparison across tests. We also used a multivariate regression method involving generalized estimating equations (GEE) that specifies the 3 standardized scores from the cognitive tasks as a single vector of outcome. The advantage of GEE is that covariates with similar effects across domains can be modeled simultaneously, allowing for more precise estimates of coefficients. Also, a correct inference can be drawn through robust variance estimates, even when the correlation structure is incorrectly specified. This technique allowed us to measure the effect of increasing WMHV or the presence of SI, on cognitive performance on all tests simultaneously. If the effect of variables, including WMHV and SI, varied across domains then interaction terms with each domain were included in the models. Because the location of SI may affect performance in specific cognitive domains, we grouped SI by frontal, deep (caudate; basal ganglia; internal, external, and extreme capsules; thalamus), and occipital-temporal-parietal locations from a total of 17 visual ratings of location.

Results

Sample Characteristics

Neuropsychological and brain imaging data were available for 656 participants. The sociodemographic characteristics of the subsample differed from the overall NOMAS cohort in that there were fewer women (58 versus 63%), more Hispanics (58% versus 54%), and slightly fewer Black (21% versus 25%) and White (18% versus 21%) participants. As is typical of brain imaging studies that are limited to subjects who can travel for evaluation, the sample was somewhat healthier than the overall cohort with a lower prevalence of hypertension (67% versus 74%), diabetes (17% versus 21%), and cardiac disease (17% versus 24%). The characteristics of the study sample are presented in Table 1. One hundred four participants had SI (frontal=25, deep=51, occipital-parietal-temporal=16, mixed=12).

We compared performance on the tests of sequencing, cognitive flexibility, and sensorimotor ability for those with increasing quartiles of WMHV (Table 1) as well as those with and without SI. In an unadjusted analysis we found a linear inverse association between increasing WMHV quartiles and performance on all 3 tests, and those with SI performed worse on all 3 tests as well. Adjusting for age and education there was an inverse linear association between increasing quartiles of WMHV and performance on the tests of cognitive flexibility (Color Trails 2) and sensorimotor ability (Grooved Pegboard) but not the test of sequencing (Color Trails 1). Those with SI performed worse on all 3 tests, adjusting for age and education (see Table 1).

Correlation in performance among the cognitive tests was moderate to high (Correlation coefficients: Grooved Pegboard with Color Trails 1=0.5; Grooved Pegboard with Color Trails 2=0.5; Color Trails 1 with 2=0.7). We therefore used

Table 2. Association Between Subclinical Brain Disease and Performance on Tests of Sensorimotor Ability, Sequencing, and Cognitive Flexibility Using Generalized Estimating Equations (GEE)*

	Grooved Pegboard			Color Trails 1			Color Trails 2		
Subclinical Brain Disease	β*	95% CI	P	β	95% CI	P	β	95% CI	P
Log-WMHV	−0.13	(−0.22, −0.04)	0.004	−0.07	(−0.16, 0.02)	0.135	−0.10	(−0.18, −0.02)	0.016
WMHV quartiles									
Quartile 4	−0.30	(−0.52, −0.07)	0.010	−0.11	(−0.32, 0.10)	0.306	−0.21	(−0.41, 0.001)	0.051
Quartile 3	−0.16	(−0.37, 0.04)	0.123	−0.10	(−0.29, 0.09)	0.309	−0.15	(−0.34, 0.05)	0.145
Quartile 2	−0.09	(−0.29, 0.11)	0.391	−0.06	(−0.25, 0.12)	0.500	−0.13	(−0.31, 0.05)	0.153
Subclinical infarcts									
Frontal	−0.23	(−0.62, 0.17)	0.255	−0.23	(−0.59, 0.14)	0.221	−0.36	(−0.67, −0.05)	0.022
Temporal-parietal-occipital	−0.15	(−0.70, 0.39)	0.584	−0.05	(−0.40, 0.30)	0.774	0.17	(−0.21, 0.55)	0.380
Deep gray matter	−0.27	(−0.56, 0.02)	0.069	−0.35	(−0.70, −0.01)	0.046	−0.24	(−0.51, 0.03)	0.086

*Adjusted for age and education.

GEE to assess performance on these tests simultaneously. We found a global association between increasing log-WMHV and worse cognitive on all the tests, adjusting for age and education (Z=−0.1, 95% CI −.2, −0.1, P=0.0006). Adjusting further for hypertension or diabetes decreased the association minimally (Z=−0.1, 95% CI −0.2, −0.03, P=0.0006).

We next explored the effect of increasing quartiles of WMHV on cognitive function. An increasing global effect across tests was evident for quartiles 3 (P=0.06) and 4 (P=0.004) compared with the lowest quartile, adjusting for age and education. Cognitive performance did not differ significantly between those with WMHV in quartile 2 and those in the lowest quartile. When we examined performance on the individual tests, we found that compared with those in the lowest quartile, individuals in the top quartile of WMHV performed significantly worse on the tests of sensorimotor ability (Grooved Pegboard) and cognitive flexibility (Color Trails 2) but not the test of sequencing (Color Trails 1), adjusting for age and education (Table 2). The results were similar using the continuous measure (log-WMHV; Table 2). The association was attenuated somewhat adjusting for hypertension and diabetes, but remained significant using either the continuous measure of WMHV or the upper quartile of WMHV compared with the lowest (data not shown).

We then considered cognitive performance for those with and without SI and found a global effect of worse cognitive performance across all tests using GEE and adjusting for age and education (Z=−0.2; 95% CI −0.4, −0.1; P=0.003). The results were similar adjusting further for a history of hypertension and diabetes. Examining cognitive performance by SI location indicated that those with SI in deep locations performed marginally worse on the test of sensorimotor function (Grooved Pegboard; P=0.07) and cognitive flexibility (Color Trails 2; P=0.09) and significantly worse on the test of sequencing (Color Trails 1; P=0.05), whereas those with SI located in the frontal region performed significantly worse on the test of cognitive flexibility (Color Trails 2; P=0.02, Table 2), adjusting for age and education. Adjusting for hypertension and diabetes resulted in slight attenuation of the association between frontal SI and cognitive flexibility and deep SI and sequencing, cognitive flexibility, and sensorimotor ability.

Considering WMHV and SI together, both were associated with worse cognitive performance globally. In addition, the effect of WMHV on sensorimotor ability remained (Grooved Pegboard, 4th Quartile Z score=−0.3, 95% CI −0.5, −0.03; P=0.026) but the association with cognitive flexibility was attenuated (Color Trails 2, 4th Quartile Z score=−0.2, 95% CI −0.4, 0.03; P=0.097). Also, the effect of frontal SI on cognitive flexibility was no longer significant, but the association between deep SI and cognitive performance remained for the test of sensorimotor ability and the test of cognitive flexibility (data not shown).

Discussion

In separate analyses we found that WMHV and SI were each associated with worse cognitive performance globally on tests of sensorimotor ability, sequencing, and cognitive flexibility. The effect of WMHV on cognition appeared to be dose-related because increasing quartiles were associated with worse performance and the fourth quartile had the strongest effect. For those with SIs, location was important; deep lesions were associated with impaired performance to some degree on all 3 cognitive tests, whereas frontal infarcts were related to less cognitive flexibility. Adjusting for conventional vascular risk factors resulted in slight attenuation of these effects, suggesting that our measures of subclinical cerebrovascular damage are in the causal pathway between vascular risk factors and cognitive dysfunction.

The volume of white matter hyperintensities sufficient to cause cognitive problems in populations without stroke is unknown. We found that having a WMHV in the upper quartile (0.75% of cranial volume) was associated with poorer performance on tests of sensorimotor ability and cognitive flexibility. Population-based studies have found an association between WMH, processing speed, and executive function but few studies have examined sensorimotor ability.[9] Though quite limited by small sample sizes, the few studies that have examined this domain have not found an association with WMH even though associations with measures of executive function and psychomotor speed have at the same

time been present to varying degrees.[9,20] An Australian population-based study in subjects aged 60 to 64 did find that both sensorimotor ability (termed "motor dexterity") and choice reaction time were inversely associated with WMH.[11] However, these studies did not use statistical methods accounting for the correlation among covariates with shared effects. Thus, when an association is found for several tests it is not clear how much the variance is shared. We hypothesized that the Grooved Pegboard might be a robust marker of white matter damage because it is sensitive to cerebral dysfunction in normal individuals and is impaired in younger subjects with WMH.[11] The effect of WMH on cognitive performance in our study may be caused by slow neural transmission or conduction along important integrative rostral-caudal pathways. This in turn could result in decreased psychomotor speed.[6] Both somatosensory and visual evoked potentials can be slowed in the presence of WMH.[21,22]

Subclinical infarcts were also associated with worse cognitive performance, and location was important. Deep infarcts affected all test results to some degree, especially sequencing, supporting the view that subcortical infarcts cause psychomotor slowing. Having SI in the frontal region on the other hand was linked to cognitive flexibility but not tests of sequencing and sensorimotor ability, suggesting a different effect on tasks of executive function that involve shifting mental sets and may depend more on dorsolateral prefrontal cortex. The effect on executive function was attenuated when we adjusted for both WMHV and SI suggesting that disruption of frontal-subcortical circuits by either SI or WMH affects frontal lobe function. White matter hyperintensities mediate activation of dorsal-lateral prefrontal cortex and reduce performance on tasks of working memory, and SI in the frontal region may disrupt frontal-subcortical circuits.[23,24]

We acknowledge evident limitations of this study. The cross-sectional design prevents a determination of causality between WMH severity and cognitive performance. We adjusted for potential confounders of cognitive performance, including sociodemographic and vascular risk factors in our global analyses. However, a larger sample is needed to clarify the effects of these factors on performance on the individual tests. We did not examine racial or ethnic differences in cognitive performance for 2 reasons. First, any associations would be difficult to interpret because race and ethnicity are often surrogates for socioeconomic status. Also, other factors that may influence cognitive performance such as literacy are not captured by years of educational attainment and may differ by race or ethnicity.[25] Second, the sample is not large enough to evaluate each analysis by race or ethnic group. Separating the effects of the 2 types of subclinical imaging findings is not possible in a study of this type because there is considerable overlap; 32% of those in the upper quartile of WMHV had subclinical infarcts. Our findings remained significant for WMHV excluding subjects with SIs and for subjects with SIs eliminating those in the upper 2 quartiles of WMHV. We do not have data on WMHV by brain region. However, location may not be as critical for WMH as it appears to be for SI. Data from positron emission tomography show that WMHs impair frontal lobe function regardless of topographical location.[26] For the determination of WMHV, we used methods that currently have only research application. However, the study of WMH and cognition is in its early stages and our methods are in keeping with recent harmonization standards for research on vascular cognitive impairment (VCI) promulgated by the NINDS and Canadian Health Network.[27]

In conclusion, WMHV and SI were associated with worse performance on 3 timed cognitive tasks. We found a threshold effect for WMHV: individuals having a WMHV greater than 0.75% of total cranial volume (fourth quartile) performed worse than those in the lowest quartile on 2 tasks. In addition, subclinical infarcts in the frontal region showed an effect on cognitive flexibility whereas deep infarcts were linked to psychomotor speed.

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